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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/854,140	05/11/2001	Hans H. Schiffer	SALK2940 (088802-8051)	6799

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EXAMINER	
SAKELARIS, SALLY A	
ART UNIT	PAPER NUMBER
1634	10

DATE MAILED: 11/06/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/854,140	SCHIFFER ET AL.	
	Examiner	Art Unit	
	Sally A Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *14-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Arguments

Election/Restrictions

Applicant's arguments filed 9/03/02 have been fully considered but they are not persuasive. Applicant's election with traverse of Group I, claims 1-13 in paper No. 9 is acknowledged. The traversal is on the ground(s) that the examiner could, without undue burden on his time or searching efforts, search and examine all pending claims in the application and that no conservation of PTO resources would be realized if the restriction requirement into six Groups is maintained. Examiner purports that the fact that each Group's classification is different, serves as prima facie evidence that the search would in fact be burdensome. Although the search for groups I-VI may have a small overlap, the search in its entirety of each group is much broader and more extensive than alleged by the applicant. In response to applicant's arguments concerning Groups I-III, the method of Group I is not structurally limited to the intended use of the kits in Groups II and III. Groups I and II are related by product and process of use and each can be used in different embodiments, while I and III are patentably distinct because the method of detecting the genotype does not require the antibody and the antibody does not require the method. With respect to Groups IV and V, it is maintained that the protocols and reagents required for administering a compound to a subject are materially distinct and separate than those required for identifying the compounds using cells expressing GluR7. With respect to Groups V and VI, it is further maintained that the protocols and reagents required for incubating cells and a compound *in vitro* and for transgenics are materially distinct and separate.

Examiner reiterates that the vastly different status acquired by each group in the art would require an undue search burden including different keyword searches extending into a wide variety of databases. The restriction requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of determining predisposition of a human subject to recurrent unipolar depressive disorder by determining in a brain tissue sample or a genomic DNA sample of a human subject, the presence of a kainate receptor subunit GluR7 allelic genotype of homozygosity for a thymine containing nucleotide at position 928 (928T/T), does not reasonably provide enablement for (i), a method of determining predisposition of any subject to any mood

disorder by detecting any GluR7 allelic genotype or phenotype or (ii), a method comprising determining in a biological sample of a subject, the presence of a kainate receptor subunit GluR7 allelic genotype or allelic phenotype wherein said allelic genotype is homozygosity for a guanine containing nucleotide position 928 (928G/G) and is associated with bipolar II depressive disorder or (iii), wherein said allelic phenotype is homozygosity for a serine at amino acid position 310 (310Ser/Ser) or homozygosity for an alanine at position 310 (310 Ala/Ala) and their association with recurrent unipolar depressive disorder and bipolar II depressive disorder respectively or (iv), methods for determining predisposition to a mood disorder by detecting a predominance in expression of either the T or G allele at position 927 of the GluR7 gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims 1-7 are broadly drawn to a method of determining predisposition of a subject to a mood disorder, said method comprising determining in a biological sample of a subject, the presence of a kainate receptor subunit GluR7 allelic genotype or allelic phenotype associated with predisposition to a mood disorder. The specification teaches a method of determining predisposition of a human subject to recurrent unipolar depressive disorder by determining in a brain tissue sample or a genomic DNA sample of a human subject, the presence of a kainate receptor subunit GluR7 allelic genotype of homozygosity for a thymine containing nucleotide at position 928 (928T/T). The specification further teaches a predominance of this 928T/T genotype in people affected with recurrent unipolar depressive disorder occurring at a frequency of 60.4%(Table 3) and further teaches a predominance of the "T" allele as being present at a frequency of 77.7%(Table 4) in the 153 families that were tested. Additionally, the credibility of

the latter allele frequency of 77.7% was substantiated by the specification through the provision of a statistically relevant p-value of 0.057. The specification has not established a clear correlation between the G/G genotype and the occurrence of bipolar II depressive disorder. The specification at page 49 states that the G allele is present at an increased frequency in bipolar II disorders. However, Table 3 shows that the G/G genotype is present in about 10% of bipolar II patients, whereas the T/T genotype is present in 39% of bipolar II patients. Table 4 shows that the T allele is present in about 65% of bipolar II affected offspring and the G allele is present in about 35% of bipolar affected offspring (with a less than significant p-value of 0.180). It is noted that the art teaches that "data analyzed using the chi-square test uses $p < 0.05$ to be considered statistically significant."(Digestive Diseases and Sciences, 1998) Furthermore, the specification refers generically to bipolar II disorders and not to bipolar II depressive disorder. It is unclear as to whether the data provided in Tables 3 and 4 is based on the findings obtained with all bipolar II patients or is based on the findings obtained with bipolar II depressive disorder patients. The specification does not teach a method broadly drawn to determining predisposition of a subject to a mood disorder, said method comprising determining in a biological sample of a subject, the presence of a kainate receptor subunit GluR7 allelic genotype or allelic phenotype associated with predisposition to a mood disorder. Furthermore, the specification does not teach wherein said allelic genotype is homozygosity for a guanine containing nucleotide position 928 (928G/G) to be associated with bipolar II depressive disorder. Table 3 omits any teachings of a correlation between the genotype distribution frequency of "G/G" and its association with bipolar II depressive disorder.

With respect to claims 8-13, they are broadly drawn to a method of determining the predisposition of a subject, having a T/G heterozygosity at nucleotide position 928 in the GluR7 gene, to a mood disorder, said method comprising determining in a biological sample of a subject, a predominance in the expression of either the T allele or the G allele. As stated previously, the specification teaches a method of determining predisposition of a human subject to recurrent unipolar depressive disorder by determining in a brain tissue sample or a genomic DNA sample of a human subject, the presence of a kainate receptor subunit GluR7 allelic genotype of homozygosity for a thymine containing nucleotide at position 928 (928T/T). However, the specification does not teach a method wherein either the mRNA or protein levels of expression of the T or G alleles of the human GluR7 gene predispose a subject to a mood disorder. The specification does not teach definitively that the unequal expression of either the T or G alleles is strictly correlated. In fact, table 2 of the specification teaches that the majority(32/41) of GluR7 allele expression level differences fell within the less than two fold difference category, while only 9/41 were between 2-12.7 fold differentially expressed. In addition, neither the T or G allele were expressed in a manner consistently(ie, sometime T was expressed less and other times G was expressed less –see page 41 of the specification).

As stated in *Vaek* (20 USPQ2d 1438), the specification must teach those of skill in the art how to make and how to use the invention as *broadly* as it is claimed" (emphasis added). The amount of guidance needed to enable the invention is related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher* 427 F. 2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Predictability or lack thereof in the art refers to the ability of one of skill in the art to extrapolate the disclosed or known results to the invention that is claimed. If

one of skill in the art can readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is unpredictability in the art. With respect to the present invention, one cannot readily anticipate one cannot readily anticipate a method of determining predisposition of a subject to a mood disorder, said method comprising determining in a biological sample of a subject, the presence of a kainate receptor subunit GluR7 allelic genotype or allelic phenotype associated with predisposition to a mood disorder. One cannot anticipate what subject is being studied(ie. human, rat, etc.), what specific mood disorder(ie. bipolar I, bipolar II, etc.) is being predetermined, or generally what allelic genotype or allelic phenotype is associated with this predisposition. It is noted that the claims are broadly drawn to methods which detect any allelic variant of the GluR7 gene. However, the specification only addresses an association between T/T homozygosity at position 928 and recurrent unipolar depressive disorder. There are no teachings in the specification regarding other possible alleles that may be associated with mood disorders. In the absence of specific guidance as to the identity of other mutations in the gluR7 gene frequency of occurrence of these alleles in other known mood disorders, it would require undue experimentation to analyze the GluR7 gene for additional alleles that may be associated with mood disorders to obtain a method for diagnosing mood disorders by detecting any allelic genotype or phenotype of GluR7. Additionally, the results obtained with recurrent unipolar depressive disorder cannot be extrapolated to all mood disorders. The unpredictability in the art is emphasized by the teachings in the Applicant's specification regarding a lack of association between the mutation at 928 and other mood

disorders. For example, in that the specification teaches that bipolar I disorder is not correlated with the T/T, G/T or G/G genotypes (See Table 3). Additionally one is unable to anticipate the specific association between the presence of the "G" allele and a predisposition to bipolar II disorder, as portrayed in Tables 3 and 4 since the p-value is far above the art's traditionally observed, standard of significance of about 0.05. The specification itself also provides much uncertainty with respect to the claimed correlations. While on page 39, the specification teaches that the GluR7 alleles are unequally represented in most of the RT-PCR product fractions originating from brain tissue samples of nine individuals and further that the unequal expression of GluR7 mRNA was also detected when the temporal lobes of neuropsychiatric patients was analyzed. The specification continues on pages 40 and 41 to contrast these previous findings, by teaching that in "27 brain samples that showed unequal expression of on GluR7 allele was not strictly correlated with a particular nucleotide type (T or G) found at the T/G site, although the T allele had a lower expression level than the corresponding G allele." The specification goes on to teach the while "18 brain samples derived from 16 brains showed a lower expression of the T allele, in contrast to nine brain samples derived from six brains that showed a lower expression of the G allele"(Table 2). The post-filing date art corroborates the unpredictability in the art by teaching that much uncertainty exists in the potential for correlating the T/G nucleotide variation at position 928 in the human kainate receptor gene, GluR7 with changes in its expression that are indicative of a predisposition to a mood disorder(Schiffer et. al 2000, abstract). This piece of post-date art reveals that the analysis of 41 tissue samples obtained from 30 human brains, revealed expression level differences between GluR7 alleles expressed in the same brain. Furthermore, "the expression level of the allelic GluR7 mRNAs differed in 27 samples from 1.2-

12.7 fold." Additional uncertainty can be found in the art's teaching that traditionally, the problem of unequally expressed allelic mRNAs due to genomic imprinting can be resolved by the conservation of such gene expression between humans and mice. However, the art taught that contrary to most cases, the detection of unequal expression of allelic GluR7 mRNAs in mice does not occur. With respect to the present invention, one cannot readily anticipate the to what mood disorder a certain subject could be predisposed to by the presence of just any allelic genotype or allelic phenotype. Such random trial by error experimentation is considered to be undue and in view of the high level of unpredictability in the art and the lack of guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

The specification provides no guidance as to how to predictably identify additional samples wherein the claimed allelic genotypes and phenotypes are consistently correlated to a certain mood disorder. Furthermore, the specification fails to teach how these allelic phenotypes actually result in any of the claimed mood disorders seeing as, previously stated, the expression levels of the mRNA was quite unpredictable. Consequently, the resulting protein levels will be similarly variable and unpredictable, making the comparison of protein expression between the Serine containing GluR7 and the alanine containing GluR7 require undue experimentation. The ability to establish a correlation between the presence of a kainate receptor subunit GluR7 allelic genotype or allelic phenotype and the occurrence of any mood disorder is highly unpredictable and can only be determined through extensive, random, trial and error experimentation. Therefore, neither the specification nor the art provides the guidance necessary to distinguish between different genotypes and phenotypes and their alleged association with any mood

disorder. In view of the high level of unpredictability in the art and the lack of guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

PRIOR ART

Claims 1-13 are free of the art.

Any inquiry concerning this communication or earlier communication from the examiner should be directed to Sally Sakelaris whose telephone number is (703) 306-0284. The examiner can normally be reached on Monday-Thursday from 6:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W.Gary Jones, can be reached on (703)308-1152. The fax number for the Technology Center is (703)305-3014 or (703)305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantae Dessau whose telephone number is (703)605-1237.

Sally Sakelaris

10/30/20002

CARLA J. MYERS
PRIMARY EXAMINER